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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Tian-Li Wang

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BANNER & WITCOFF

1001 G STREET N W

SUITE 1100

WASHINGTON, DC 20001

EXAMINER

MCGILLEM, LAURA L

ART UNIT

PAPER NUMBER

1636

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/705,874	Applicant(s) WANG ET AL.	
	Examiner Laura McGillem	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 2/16/2006.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-91 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 90 is/are allowed.
- 6) ☒ Claim(s) 1-89 and 91 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 13 November 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>2/16/2006</u> | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

It is noted that claims 1, 25-37, 59, 62-35 and 75-80 have been amended and claims 86-91 have been added in the amendment filed 2/16/2006.

Claims 1-91 are under examination.

Information Disclosure Statement

It is noted that an information disclosure statement (IDS) was submitted on 2/16/2006. The information disclosure statement has been considered by the examiner.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. See paragraphs 0033, 0037 and 0039. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 59-85 and 91 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to

one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a NEW MATTER rejection.

Independent claims 59 and 75 have been amended so that the phrase “comparing the number of pieces enumerated within each of the plurality of windows” now recites, “comparing a first number of pieces enumerated within *one* of said windows”. As the claims are written, they are drawn to enumerating pieces in many windows and then only comparing the number of pieces in one of the windows. The specification does not disclose the limitation of enumerating pieces within only one window in the context of enumerating the pieces within a plurality of windows. Newly added claim 91 also teaches enumerating pieces with a plurality of windows and making a comparison of the number of pieces in a window, which is a limitation not taught in the specification. Therefore, these claims contain impermissible new matter.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-24, 30-34, 37-58 and 86-89 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite because it recites the phrase “a first number which is a sum of numbers of a plurality of individual sequence tags” and it is not clear what is meant by “sum of numbers of a plurality”. Lines 6-7 recite the phrase “numbers of *individual* sequence tags” and then lines 9-10 recites the phrase “sum of numbers of

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a *plurality* of individual sequence tags” and it is not clear how the “number of a plurality of individual sequence tags” has been obtained. The metes and bounds of “plurality” are not clear. As the claim is written and with consideration of the information in Table 2 of the specification, it appears that Applicants may intend that a “numbers of *individual* sequence tags” refers to the number of copies of sequence tags in each chromosome and the sum of numbers of a plurality is a total number of all the copies of sequence tags in each chromosome and the “first number” represents the sum total of all copies of sequence tags in the entire genome, but it is not clear if this is encompassed in the claimed method.

Claims 37 and 86-89 are vague and indefinite because they recite the phrases “first number of individual sequence tags” and the “first number of a plurality of sequence tags” and the metes and bounds of “first number” are not clear since a first number can be a number of individual sequence tags and a number of a plurality of sequence tags. Furthermore, a limitation of each of these claims is “wherein a difference between the first number and the second number indicates a karyotypic difference” and it is not clear which “first number” should be used to determine the difference; the “first number of individual sequence tags” or “first number of a plurality of sequence tags”. Claims 37 and 86-89 do not specify a number of a plurality of *individual* sequence tags. It is not clear how the “number of a plurality of sequence tags” has been obtained. It is not clear if one of the “first numbers” refers to a total number or number of copies of sequence tags.

Claims 30-33 are vague and indefinite because they have been amended to recite the phrase "concatamers of dimers made by the process of ligation of dimers in the isolated population according to claim" 25 or 26 or 27 or 28, and it is not clear whether the Applicants intend that the dimers are "according to claim 25" or the process of ligation" is according to claim" 25 or 26 or 27 or 28. Claims 25-28 are drawn to dimer populations and not processes of ligation.

Claims 1, 37 and 86-89 recite the limitation " the genome of the species " in line 13. There is insufficient antecedent basis for this limitation in the claim. The claims recite "genome of a test eukaryotic cell", "genome of the eukaryotic cell" and "genome of a reference cell". The claims do not recite particular species, so it is unclear which species are being referred to by the phrase "the species".

Claims 2-24 and 36-58 are indefinite insofar as they depend from claims that have been rejected as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 25-34 and 36 are rejected under 35 U.S.C. 102(b) as being anticipated by Israel (U.S. Patent No. 5,981,190, of record).

Israel teaches formation dimers or ditags from genomic DNA of human eukaryotic cells (see column 3, lines 52-59, for example). Israel teaches that genomic DNA can be fractionated into smaller fragments by cleaving with enzymes that cleave DNA based on methylation state or condensation state. The smaller DNA fragments are then cleaved with an anchoring enzyme, ligated on to a linker sequence that includes a Type IIS endonuclease recognition site and then cleaved with a Type IIS endonuclease (second tagging enzyme). Israel teaches that cleavage with a Type IIS endonuclease occurs at a defined distance of ~20 bp from the recognition site to produce a linker-Tag fragment. Israel teaches that the cleavage with the anchoring enzyme and the tagging enzyme produces a tag of a defined length (see column 5, lines 9-11). Israel teaches that one of two different linker sequences can be added to the DNA fragments to produce two different pools of linker-Tag fragments, which can then be combined and ligated to form head to head ditags or dimers which are joined at the end of the linker-Tag fragment opposite from the linker or Type IIS endonuclease end. Israel teaches that this group of ditags can be used as PCR templates (see column 6, lines 3-12 and Figure 2B, in particular). Therefore, Israel teaches an isolated population of dimers wherein each dimer comprises two distinct sequence tags from portions of a eukaryotic cell genome that are defined by two restriction endonuclease recognition sites, consisting of a fixed number of nucleotides extending from the Type IIS endonuclease recognition site, wherein the other end of the tag is defined by the first restriction enzyme. Further, Israel teaches that the ditags can be concatenated by ligation (see

column 3, lines 40-50 and column 6, lines 20-24), therefore Israel teaches a concatamers of dimers made by the process of ligation of the claimed dimers.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 37-38, 42, 47-50, 52, 56 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 6,498,013 (Velculescu et al, of record), filed 7/27/2001, in view of Dunn et al (Nov. 4, 2002, of record). Rejections of claims 5, 15, 29, 40-41, 61, 71, 75-76, 81 and 85 under 35 U.S.C. 103(a) are withdrawn. Claims 47-50 are dependent on the method of claim 37 and have been newly added to this rejection.

This rejection is being maintained for reasons of record in the previous Office action (mailed 11/16/2005) and for reasons outlined below.

Applicants submit that all of the rejected claims (except claim 29) have been amended or their independent claim has been amended to require that less than 100% of the sequence tags or pieces of genomic DNA calculated to be present in the genome of the eukaryotic cell are enumerated. Applicants submit that Dunn does not teach this element. Applicants submit that Dunn teaches redundant sampling of his genome signature tags, i.e., he teaches more than 100% sampling because Dunn teaches

enumeration of 417% of the sequence tags or genomic fragments which are calculated to be present. Applicants submit that Dunn does not teach or suggest any method by which less than 100% enumeration could be accomplished to provide useful results. Applicants submit that Velculescu also does not teach this element. Applicants submit that the cited combination of references fails to establish *prima facie* case of obviousness for the claims as amended. Applicants submit that Dunn et al do not teach the use of dimers and that Velculescu et al teach dimers but not of genomic DNA, but there is no suggestion or teaching in Dunn that dimers should be used.

Applicants submit that the term "window" as used in the claim does not read on a concatamer of random sequence tags. Applicants submit that windows are analytical constructs that encompass tags which are contiguous in the genome of the eukaryotic cell. Random tag concatamers may be contiguous in a particular clone, but that does not make them contiguous in the genome.

Applicant's arguments filed 2/16/2006 have been fully considered but they are only partially persuasive.

Velculescu et al teach that computer analysis of human pancreas transcripts revealed 84,300 sequences. Velculescu et al teach further analysis was performed using a SAGE database analysis program set to include only sequences noted as "RNA" in the locus description and to exclude entries noted as "EST", which resulted in a reduction of the 84,300 sequences to 13,241 sequences. Velculescu et al analyzed this 13,241 subset of sequences using NlaIII as the restriction enzyme and indicated that 4,127 tags were unique while 1,511 tags were found in more than one entry.

Velculescu et al suggested that 5381 of the 9 bp tags were unique to a transcript or highly conserved transcript family. Further, Velculescu et al exemplify the method of serial analysis of gene expression (longSAGE) method and only analyze the first 1000 tags (see column 15, lines 30-67, for example). Analysis of 1000 tags out of ~5381 tags is enumeration of ~18% of the sequence tags calculated to be present. Therefore, Velculescu et al does teach a method wherein less than 100 % of the sequence tags calculated to be present in the genome of the eukaryotic cell are enumerated.

Although Dunn does not teach the use of dimers, Velculescu et al do teach the use of dimers. As described in the previous Office action, Velculescu et al teach a longSAGE method for human genomic data comprising analysis of long sequence tags defined by endonuclease recognition sites that were generated from human mRNA for the purpose of quantitative comparison of expressed transcripts in a variety of normal and disease states (see column 3, lines 1-5, for example). Velculescu et al generate dimerized tags, or ditags, comprising two sequence tags from a eukaryotic cell from endonuclease recognition sites consisting of 17-21 nucleotides extending from the restriction endonuclease recognition sites which are concatamerized and cloned for sequencing (see column 2, lines 40-67, for example).

Velculescu et al do not teach production of sequence tags from genomic DNA. Although Dunn et al teach the use of monomeric tags, the method of Velculescu et al used dimerized tags. The claimed method is obviated by modification of the method of Velculescu et al to examine genomic DNA from eukaryotic human test cells to compare to the number of sequence tags that are predicted to be present in the human genome,

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because Dunn et al teach the use of eukaryotic cells and that the longSAGE method can be easily modified to obtain genomic sequence tags by starting with genomic DNA fragments rather than poly(A)⁺ derived cDNA (see page 1763, left column, 1st full paragraph).

Although Dunn et al may not contemplate the use of dimers; Velculescu et al teach that the advantage of using ditags is a means to eliminate potential distortion introduced by the PCR amplification step on monomeric tags (see column 6, lines 8-17, for example). The method of Velculescu et al uses dimerized tags in the method as an improvement over possible monomer tag amplification distortions and Dunn et al does not need to use or suggest dimers in order to combine the methods. The methods of Dunn et al and Velculescu et al do not need to match exactly in order to render the inventive method obvious. Therefore, it would still be obvious to modify the method of Velculescu et al to use genomic DNA from eukaryotic human test cells to determine karyotypic difference between genomic sequence tags of a test eukaryotic cell and the human genome because Dunn et al teach the use of eukaryotic cells and that the longSAGE method can be easily modified to obtain genomic sequence tags by starting with genomic DNA fragments rather than poly(A)⁺ derived cDNA (see page 1763, left column, 1st full paragraph).

Claims 25-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 6,498,013 (Velculescu et al, of record), filed 7/27/2001, in view of Dunn et al (Nov. 4, 2002, of record).

Applicants claim an isolated population of dimers comprised of two distinct sequence tags from defined portions of the genome defined by one or two restriction endonuclease recognition sites consisting of a fixed number of nucleotides of said defined portions of the genome extending from at least one of the endonuclease sites. Applicants claim the dimer population wherein said portions are defined by a first restriction endonuclease site at a first end of each portion and a second restriction endonuclease site at a second end of each portion, wherein the two sequence tags are joined end-to-end at the ends distal to the second restriction endonuclease site and further comprising a linker oligonucleotide ligated at each second restriction endonuclease site of the two sequence tags. Applicants claim the dimer population wherein the fixed number of nucleotides is determined by a Type IIS restriction endonuclease MmeI is used to cleave within said defined portions of the genome and the fixed number of nucleotides is 20 to 22. Applicants further claim a concatamer of dimers made by process of ligation.

As described above, Velculescu et al teach a process of generating sequence tags, addition of an oligonucleotide linker to the end of the sequence at the site of the second restriction enzyme site so that cleavage with a tagging restriction enzyme will release a defined sequence tag and that the tags are randomly ligated to each other tail to tail, wherein the tail is the portion of the tag furthest from the oligonucleotide linker (see column 9, lines 5-35 and column 15, lines 1-20, in particular). Velculescu et al teach that the second restriction endonuclease can be a Type IIS restriction enzyme such as MmeI, to generate sequence tags of 20-22 (see column 8, lines 19-25 and

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column 21, lines 20-25, for example). Velculescu et al teach that the dimerized sequence tags can be concatamerized (see column 6, lines 1-7, for example).

Velculescu et al do not teach dimerized sequence tags generated from genomic DNA.

Dunn et al teach digestion of genomic DNA with one restriction enzyme such as NotI or BamHI, further digestion with a second restriction enzyme, such as NlaIII, to generate specific 4-bp ends, biotinylation and digestion with MmeI to generate a tag of defined length of ~21 bp (see page 1757, left column, paragraphs 1-3 and Figure 1, in particular). Dunn et al teach that the tag can be concatamerized by ligation. As mentioned above, Dunn et al does not teach dimers or concatamers of dimers.

It would have been obvious to the skilled artisan to combine the methods of Dunn et al and Velculescu et al to produce an isolated population of dimers comprised of two distinct sequence tags from genomic eukaryotic DNA and ligate them together to form a concatamers of dimers because Dunn et al teach that monomeric genomic sequence tags and a concatamers of monomeric sequence tags are useful for methods of karyotyping a eukaryotic genome and Velculescu et al teach that dimerized sequence tags and concatamers of dimerized sequence tags are useful for transcript analysis. The motivation to do so is the expected benefit of being able to eliminate potential distortions introduced by subsequent PCR amplifications and therefore dimerized sequence tags eliminate certain types of bias that might occur during cloning and/or amplification and possibly during data evaluation (see column 2, lines 49-57 and column 6, lines 8-16, in particular).

Conclusion


Claim 90 is allowable. Rejection of claims that have not been mentioned herein are hereby withdrawn.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura McGillem whose telephone number is (571) 272-8783. The examiner can normally be reached on M-F 8:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Laura McGillem, PhD
5/11/2006


DANIEL M. SULLIVAN
PATENT EXAMINER